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APPLICATION NUMBER: *60/400,064*
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60400064.080202

Atty. Dkt. No. 065691-0285

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Marco Ciufolini et al.

Title: 2-(3-amino)arylamino-4-aryl-thiazoles for the Treatment of Diseases

Appl. No.: To be assigned

Filing Date: August 2, 2002

PROVISIONAL PATENT APPLICATION TRANSMITTAL

Commissioner for Patents
Box PROVISIONAL PATENT APPLICATION
Washington, D.C. 20231

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(c) is the provisional patent application of:

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Enclosed are:

[X] Specification and Claims (62 pages).

[X] Informal drawings (2 sheets, Figures 1-2).

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Atty. Dkt. No. 065691-0285

The filing fee is calculated below:

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Basic Fee		$160.00		$160.00
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[X] A check in the amount of $160.00 to cover the filing fee is enclosed.

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Respectfully submitted,

Date Aug. 2, 2002

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2-(3-amino)arylamino-4-aryl-thiazoles for the treatment of diseases

The present invention relates to novel compounds selected from 2-(3-amino)arylamino-4-aryl-thiazoles that selectively modulate, regulate, and/or inhibit signal transduction mediated by certain native and/or mutant tyrosine kinases implicated in a variety of human and animal diseases such as cell proliferative, metabolic, allergic, and degenerative disorders. More particularly, these compounds are excellent c-kit

Tyrosine kinases are receptor type or non-receptor type proteins, which transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. These proteins are thus considered to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration as well as inflammation.

As of today, there are about 20 different subfamilies of receptor-type tyrosine kinases including the HER subfamily which are activated by several ligands comprising EGF, and TGF-a. Other tyrosine kinase are the well-known VEGF receptors (Kim et al., Nature 362, pp. 841-844, 1993), PDGF receptors, c-kit and the FLK family. These receptors can transmit signals to other tyrosine kinase including Src, Raf, Frk, Btk, Csk, Abl, Fes/Fps, Fak, Jak, Ack..etc.

Among tyrosine kinase receptors, c-kit is of special interest. Indeed, c-kit is a key receptor activating mast cells, which have been postulated to be directly or indirectly implicated in numerous pathologies for which the Applicant filed US 60/301,408, US 60/601,409, US 60/301,411, US 60/301,407, US 60/301,406, US 60/323,312, US 60/301,410, US 60/323,315, US 60/301,405, US 60/601,409, and US 60/301,404.

It was found that mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases, allergic diseases, tumor angiogenesis, inflammatory diseases, polyarthritis, inflammatory bowel diseases (IBD), and interstitial cystitis. In these diseases, it was postulated that mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators such as histamine, proteoglycans, neutral proteases), lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, GM-CSF, MIP-1a, MIP-1b, MIP-2 and IFN-γ).

The c-kit receptor also can be activated without binding its ligand SCF. A number of naturally occurring mutations lead to constitutive activation of the c-kit kinase that results in abnormal cell proliferation and the development of diseases such as mastocytosis and various other cancers.

For this reason, it has been proposed to target c-kit to deplete the mast cells responsible for these disorders.

The general problem underlying the present invention is therefore to find non toxic and selective compounds capable of inhibiting c-kit, whether they are SCF-activated c-kit inhibitors, constitutively activated c-kit inhibitors or both.

Many different compounds have been described as tyrosine kinase inhibitors, for example, bis monocyclic, bicyclic or heterocyclic aryl compounds (WO 92/20642), vinylene-azaindole derivatives (WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (US 5,330,992), Styryl compounds (US 5,217,999), styryl-substituted pyridyl compounds (US 5,302,606), seleoindoles and selenides (WO 94/03427), tricyclic polyhydroxylic compounds (WO 92/21660) and benzylphosphonic acid compounds

(WO 91/15495), pyrimidine derivatives (US 5,521,184 and WO 99/03854), indolinone derivatives and pyrrol-substituted indolinones (US 5,792,783, EP 934 931, US 5,834,504, US 5,883,116, US 5,883,113, US 5, 886,020, WO 96/40116 and WO 00/38519), as well as bis monocyclic, bicyclic aryl and heteroaryl compounds (EP 584 222, US 5,656,643 and WO 92/20642), quinazoline derivatives (EP 602 851, EP 520 722, US 3,772,295 and US 4,343,940) and aryl and heteroaryl quinazoline (US 5,721,237, US 5,714,493, US 5,710,158 and WO 95/15758).

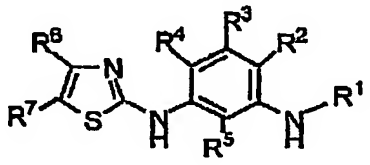
However, none of these compounds have been described as potent and selective inhibitors of c-kit or c-kit pathway.

In connection with the present invention, we have found that compounds corresponding to the 2-(3-amino)arylamino-4-aryl-thiazoles are excellent selective inhibitors of c-kit or c-kit pathway. These compounds are good candidate for treating diseases such as autoimmunes diseases, inflammatory diseases, cancer and mastocytosis.

Description

Therefore, the present invention relates to compounds belonging to the 2-(3-amino)arylamino-4-aryl-thiazoles. These compounds are capable of selectively inhibiting signal transduction involving the tyrosine phosphokinase c-kit and mutant forms thereof.

In a first embodiment, the invention is aimed at compounds of formula I:



FORMULA I

wherein R^1 is :

a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality;

b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

c) a sulfonyl or a -SO2-R group wherein R is an alkyl, aryl or heteroaryl substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

d) a -CO-NH-R, –CO-R, -CO-OR or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality;

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,

iv) H, an halogen selected from I, F, Cl or Br; NH2, NO2 or SO2;

and R^7 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, an halogen selected from I, F, Cl or Br; NH2, NO2 or SO2.

Examples of preferred compounds of formula I in which **R1** corresponds to the definition given in a) (alkyl), b) (aryl) and d) (amide) are depicted below:

AB 3001

4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3002

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide

AB 3003

4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3004

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide

AB 3005

3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3006

4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3008

4-{[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester

AB 3011

3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

AB 3014

4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3016

2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3017

4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3018

4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl}-ureido)-benzoic acid ethyl ester

AB 3020

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide

AB 3021

4-[3-(4-Bromo-phenyl)-urcido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3023

{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester

AB 3024

4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3026

4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3034

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide

AB 3035

4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3037

4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3038

4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3039

Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

AB 3040

4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

AB 3041

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide

AB 3042

3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3043

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide

AB 3044

4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3045

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide

AB 3046

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(3,4,5-trimethoxy-phenyl)-ureido]-benzamide

AB 3048

4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

AB 3049

4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

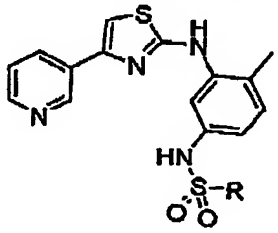
AB 3050

2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

AB 3051

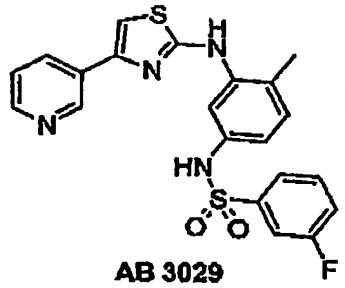
3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester

In another preferred embodiment, when R^1 has the meaning depicted in c) above, the invention is directed to sulfonyl compounds of the following formula :

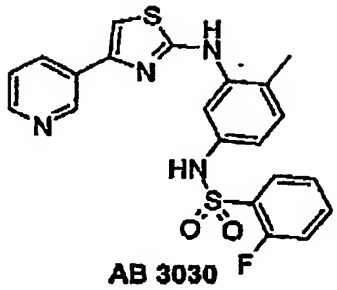


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality, or an aryl or heteroaryl group optionally substituted by an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

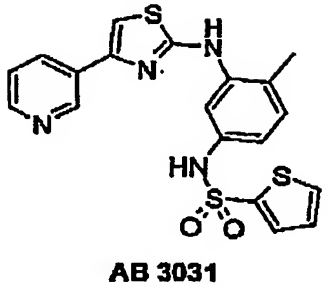
Such compounds can be selected for example from:



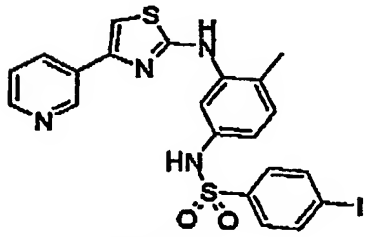
AB 3029



AB 3030



AB 3031



AB 3033

AB 3029

3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzenesulfonamide

AB 3030

2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzenesulfonamide

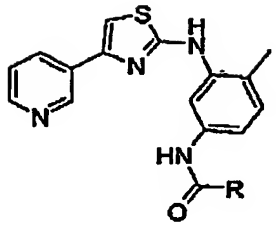
AB 3031

Thiophene-2-sulfonic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide

AB 3033

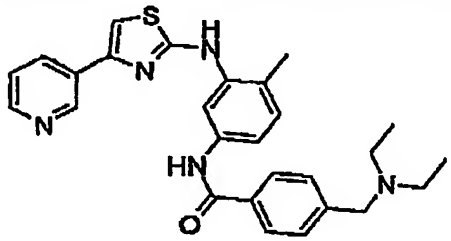
4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzenesulfonamide

In another preferred embodiment, when R^1 has the meaning depicted in d) above, the invention is directed to compounds of the following formula:

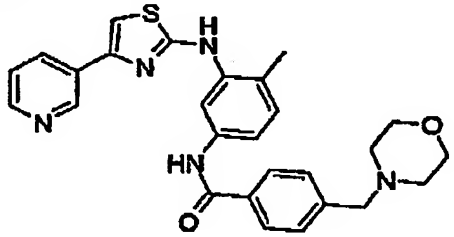


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

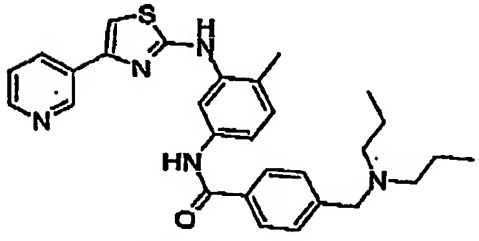
Such compounds can be selected for example from:



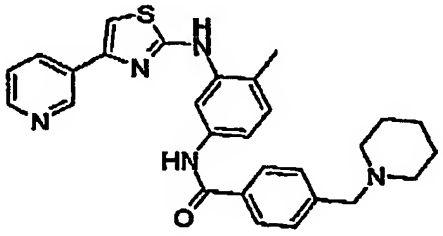
AB 3001



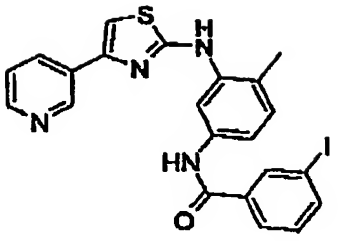
AB 3002



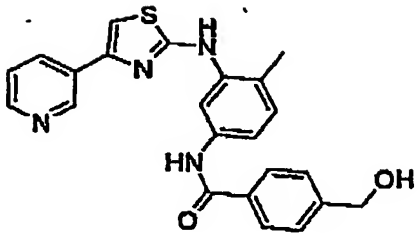
AB 3003



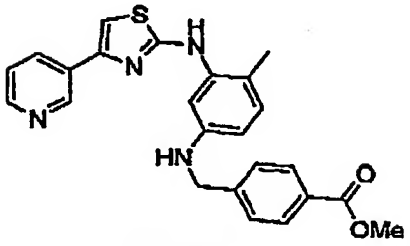
AB 3004



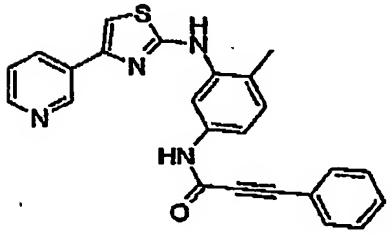
AB 3005



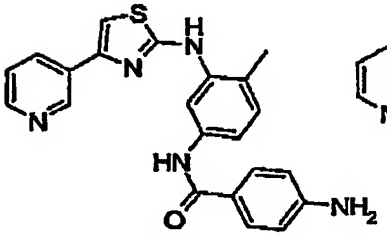
AB 3006



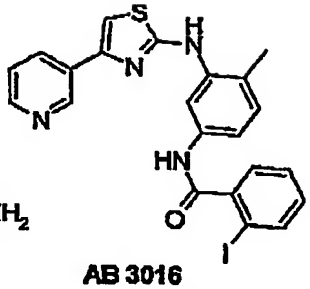
AB 3008



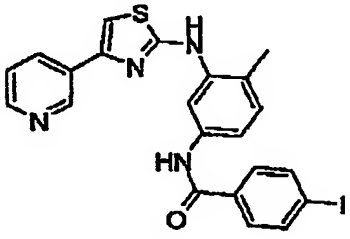
AB 3011



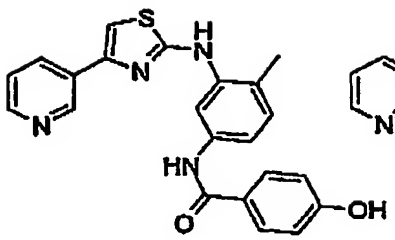
AB 3014



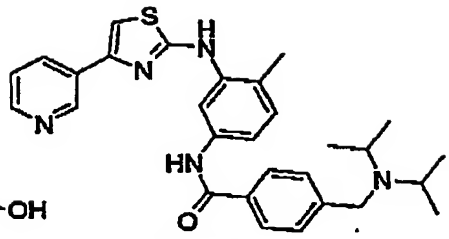
AB 3016



AB 3017

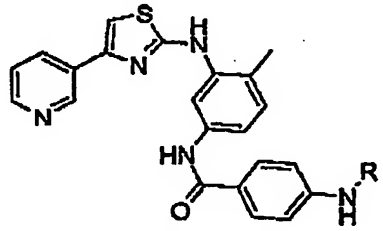


AB 3024



AB 3026

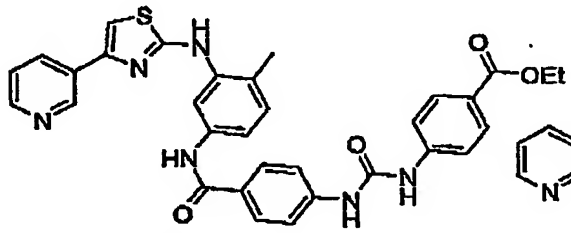
Among the particular compounds in which R1 has the meaning as depicted in d) above, the invention is directed to amide-aniline compounds of the following formula:



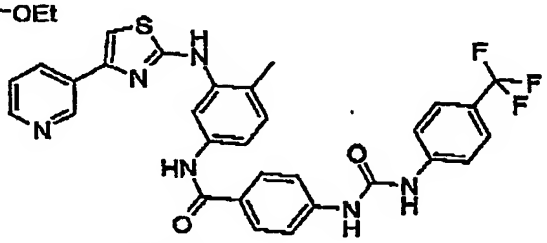
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a sulfonyl or a -SO2-R group wherein R is H, an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a -CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

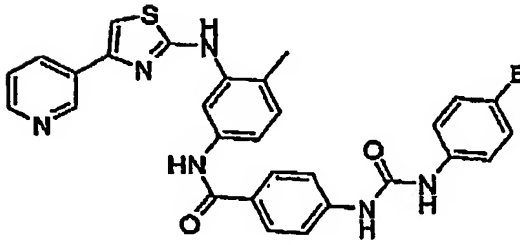
Examples of such compounds are as follows:



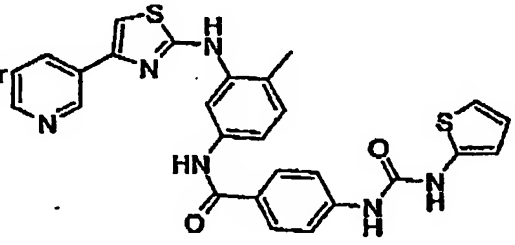
AB 3018



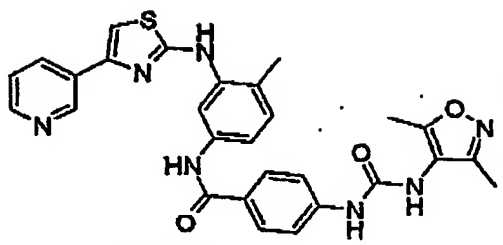
AB 3020



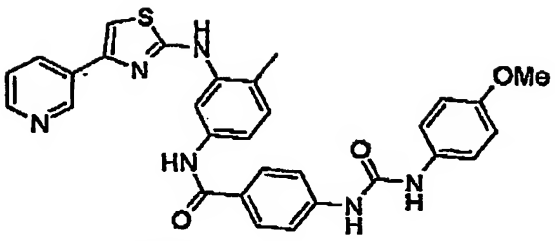
AB 3021



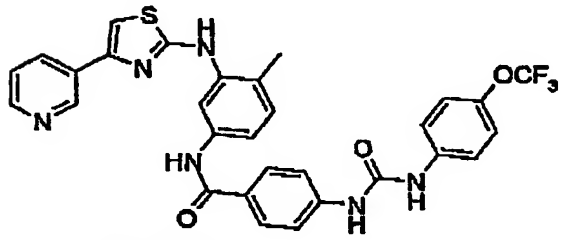
AB 3034



AB 3035

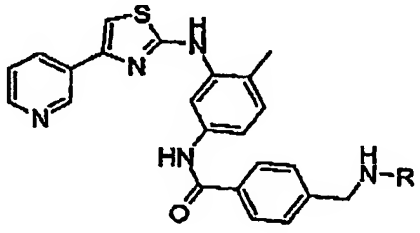


AB 3037



AB 3038

Among the particular compounds in which R1 has the meaning as depicted in d) above, the invention is directed to amide-benzylamine compounds of the following formula:

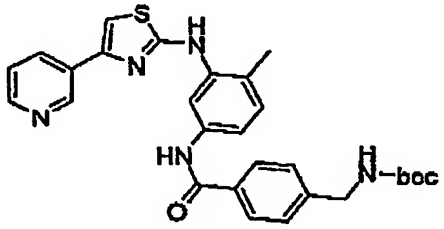


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at

least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality; a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

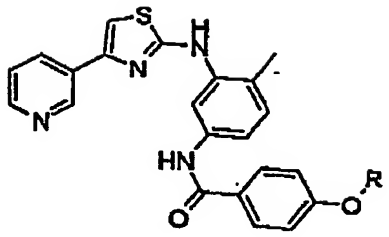
a sulfonyl or a -SO2-R group wherein R is H or an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality.

For example, this compound has the following formula:



AB 3023

Among the particular compounds in which R1 has the meaning as depicted in d) above, the invention is directed to amide-phenol compounds of the following formula:



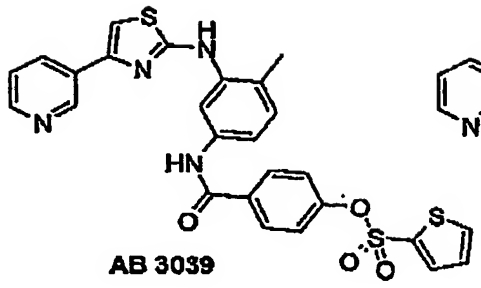
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

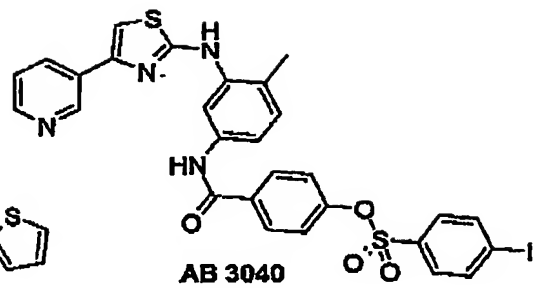
or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a sulfonyl or a -SO2-R group wherein R is H or an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality.

Examples of such compounds are as follows:

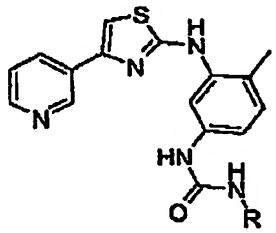


AB 3039



AB 3040

Among the particular compounds in which R1 has the meaning as depicted in d) above, the invention is directed to urea compounds of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example an halogen) or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

Examples of such compounds are as follows:

AB 3007

1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3009

1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3010

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea

AB 3012

1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3013

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea

AB 3015

4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester

AB 3019

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea

AB 3022

1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3025

1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3027

1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3028

1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3032

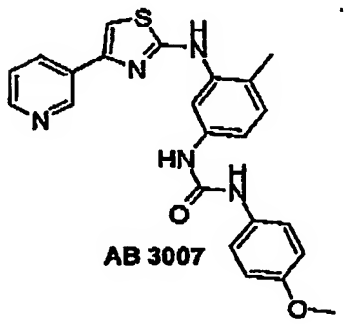
1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3036

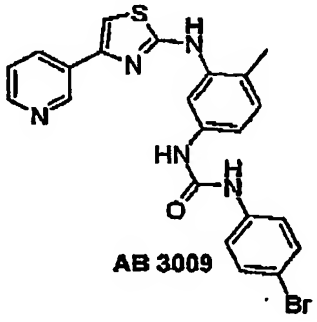
1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea

AB 3047

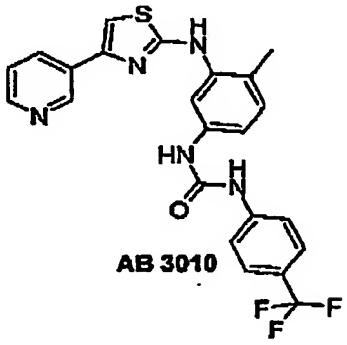
1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea



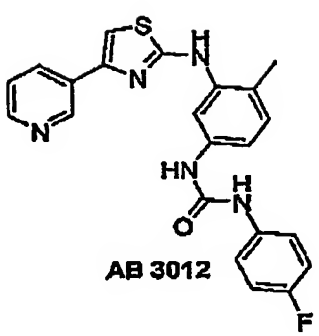
AB 3007

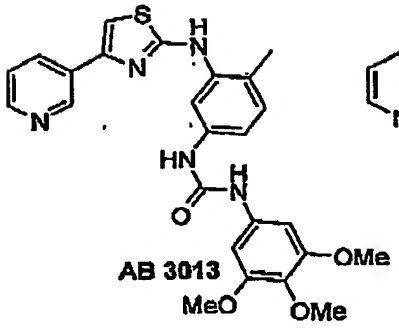


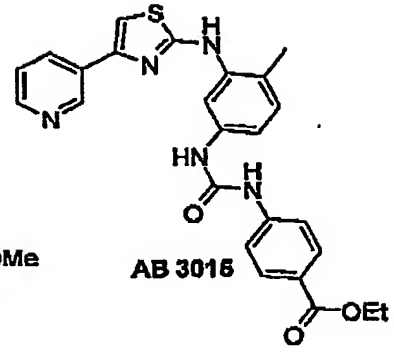
AB 3009

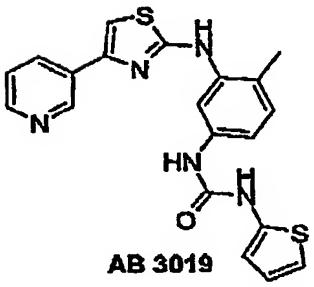


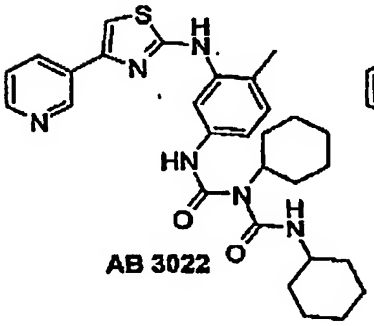
AB 3010

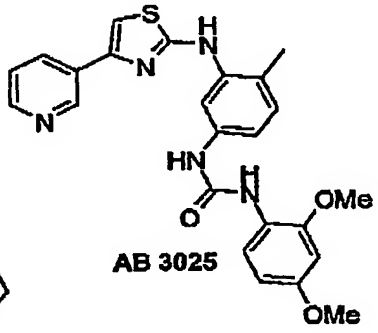

AB 3012

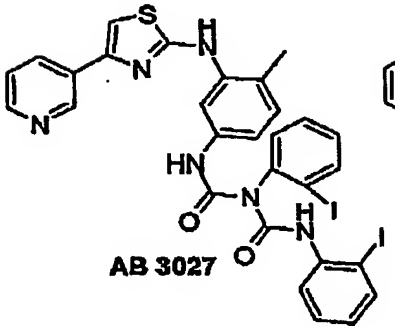

AB 3013

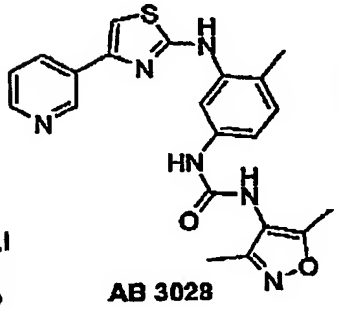

AB 3016

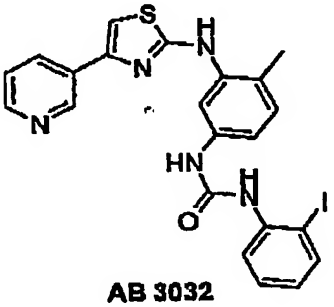

AB 3019

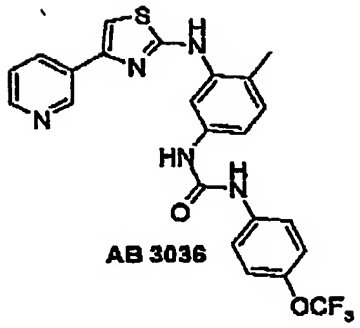

AB 3022


AB 3025


AB 3027

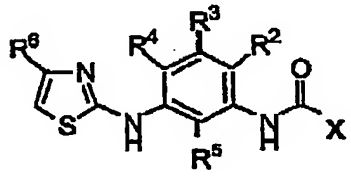

AB 3028


AB 3032



AB 3036

Among the compounds of formula I, the invention is particularly embodied by the compounds of the following formula II :



FORMULA II

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality.

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

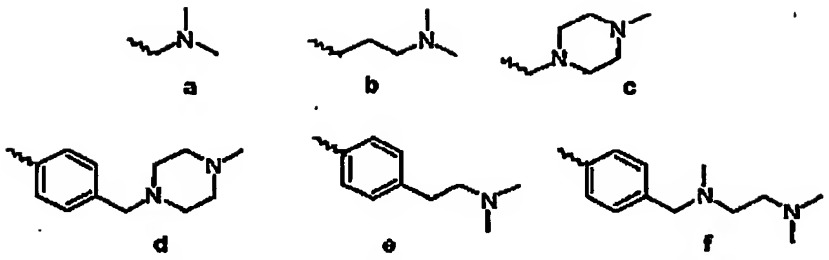
R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

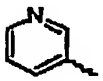
(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

Among the preferred compounds corresponding formula II, the invention is directed to compounds in which X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures a to f shown below, wherein the wavy line corresponds to the point of attachment to core structure of formula II:



Among group a to f, R^1 is preferentially group d.

Furthermore, among the preferred compounds of formula I or II, the invention concerns the compounds in which R^2 and R^3 are hydrogen. Preferentially, R^4 is a methyl group and R^5 is H. In addition, R^6 is preferentially a 3-pyridyl group (cf. structure g below) wherein the wavy line corresponds to the point of attachment to core structure of formula I or II.



Thus, the invention contemplates:

1- A compound of formula II as depicted above, wherein X is group d and R^6 is a 3-pyridyl group.

2- A compound of formula II as depicted above, wherein X is group d and R^4 is a methyl group.

3- A compound of formula I or II as depicted above, wherein R^1 is group d and R^2 is H.

4- A compound of formula I or II as depicted above, wherein R^1 is group d and R^3 is H.

5- A compound of formula I or II as depicted above, wherein R^1 is group d and R^2 and/or R^3 and/or R^5 is H.

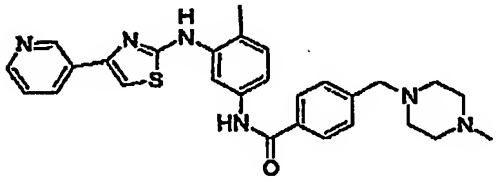
6- A compound of formula I or II as depicted above, wherein R^6 is a 3-pyridyl group and R^3 is a methyl group.

7- A compound of formula I or II as depicted above, wherein R^6 is a 3-pyridyl group and R^2 is H.

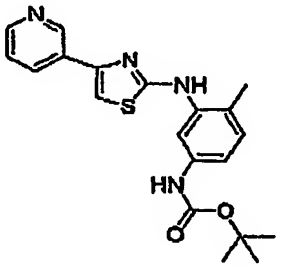
8- A compound of formula I or II as depicted above, wherein R^2 and/or R^3 and/or R^5 is H and R^4 is a methyl group.

9- A compound of formula I or II as depicted above wherein R^2 and/or R^3 and/or R^5 is H, R^4 is a methyl group and R^6 is a 3-pyridyl group.

The invention especially contemplates the compound AB-1010 (2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole) of formula :

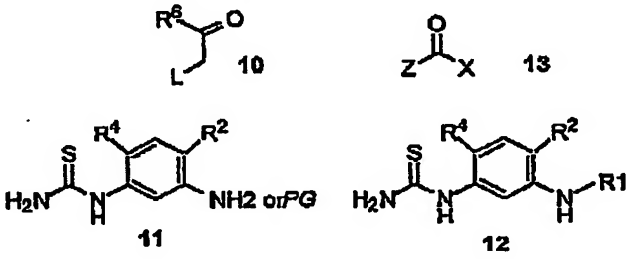


The invention also concerns the compound 2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole of formula :

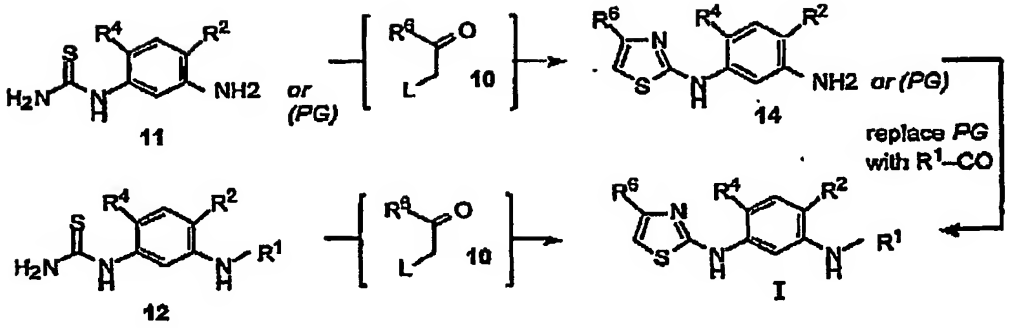


The above depicted formulas are meant to represent free-base forms of the substances described in this application as well as pharmaceutically acceptable salts thereof.

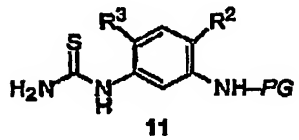
In a second embodiment, the invention is directed to a process for manufacturing a compound of formula I depicted above comprising a condensation of a derivative 10 of a methyl ketone with a thiourea of the type 11 or 12.



wherein substituent L in formula 10 is a nucleofugal leaving group active in nucleophilic substitution reactions (for example L can be selected from chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group), and wherein PG in formula 11 defines a protecting group that condensates with formula 13 to produce compounds of formula 12 and wherein it follows the synthesis flowchart to give the final product of formula I.



In frame with this process, the invention is aimed at a synthesis intermediate of formula 11 and 12, wherein R1, R2 and R3 have the same meaning as depicted above for compounds of formula I.



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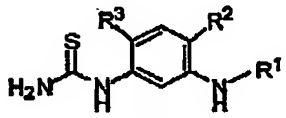


12

In a third embodiment, the invention relates to a pharmaceutical composition comprising a compound as depicted above.

Such medicament can take the form of a pharmaceutical composition adapted for oral administration, which can be formulated using pharmaceutically acceptable carriers well

known in the art in suitable dosages. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Mauck Publishing Co., Easton, Pa.).

The composition of the invention can also take the form of a pharmaceutical or cosmetic composition for topical administration.

Such compositions may be presented in the form of a gel, paste, ointment, cream, lotion, liquid suspension aqueous, aqueous-alcoholic or, oily solutions, or dispersions of the lotion or serum type, or anhydrous or lipophilic gels, or emulsions of liquid or semi-solid consistency of the milk type, obtained by dispersing a fatty phase in an aqueous phase or vice versa, or of suspensions or emulsions of soft, semi-solid consistency of the cream or gel type, or alternatively of microemulsions, of microcapsules, of microparticles or of vesicular dispersions to the ionic and/or nonionic type. These compositions are prepared according to standard methods.

The composition according to the invention comprises any ingredient commonly used in dermatology and cosmetic. It may comprise at least one ingredient selected from hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic active agents, preservatives, emollients, viscosity enhancing polymers, humectants, surfactants, preservatives, antioxidants, solvents, and fillers, antioxidants, solvents, perfumes, fillers, screening agents, bactericides, odor absorbers and coloring matter.

As oils which can be used in the invention, mineral oils (liquid paraffin), vegetable oils (liquid fraction of shea butter, sunflower oil), animal oils, synthetic oils, silicone oils (cyclomethicone) and fluorinated oils may be mentioned. Fatty alcohols, fatty acids (stearic acid) and waxes (paraffin, carnauba, beeswax) may also be used as fatty substances.

As emulsifiers which can be used in the invention, glycerol stearate, polysorbate 60 and the PEG-6/PEG-32/glycol stearate mixture are contemplated.

As hydrophilic gelling agents, carboxyvinyl polymers (carbomer), acrylic copolymers such as acrylate/alkylacrylate copolymers, polyacrylamides, polysaccharides such as hydroxypropylcellulose, clays and natural gums may be mentioned, and as lipophilic gelling agents, modified clays such as bentones, metal salts of fatty acids such as aluminum stearates and hydrophobic silica, or alternatively ethylcellulose and polyethylene may be mentioned.

As hydrophilic active agents, proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, starch and plant extracts, in particular those of Aloe vera may be used.

As lipophilic active, agents, retinol (vitamin A) and its derivatives, tocopherol (vitamin E) and its derivatives, essential fatty acids, ceramides and essential oils may be used. These agents add extra moisturizing or skin softening features when utilized.

In addition, a surfactant can be included in the composition so as to provide deeper penetration of the compound capable of depleting mast cells, such as a tyrosine kinase inhibitor, preferably a c-kit inhibitor.

Among the contemplated ingredients, the invention embraces penetration enhancing agents selected for example from the group consisting of mineral oil, water, ethanol, triacetin, glycerin and propylene glycol; cohesion agents selected for example from the group consisting of polyisobutylene, polyvinyl acetate and polyvinyl alcohol, and thickening agents.

Chemical methods of enhancing topical absorption of drugs are well known in the art. For example, compounds with penetration enhancing properties include sodium lauryl sulfate (Dugard, P. H. and Sheuplein, R. J., "Effects of Ionic Surfactants on the Permeability of Human Epidermis: An Electrometric Study," J. Ivest. Dermatol., V.60, pp. 263-69, 1973), lauryl amine oxide (Johnson et. al., US 4,411,893), azone (Rajadhyaksha, US 4,405,616 and 3,989,816) and decylmethyl sulfoxide (Sekura, D. L. and Scala, J., "The Percutaneous Absorption of Alkylmethyl Sulfides," Pharmacology of the Skin, Advances In Biology of Skin, (Appleton-Century Craft) V. 12, pp. 257-69, 1972). It has been observed that increasing the polarity of the head group in amphoteric molecules increases their penetration-enhancing properties but at the expense of increasing their skin irritating properties (Cooper, E. R. and Berner, B., "Interaction of Surfactants with Epidermal Tissues: Physiochemical Aspects," Surfactant Science Series, V. 16, Reiger, M. M. ed. (Marcel Dekker, Inc.) pp. 195-210, 1987).

A second class of chemical enhancers are generally referred to as co-solvents. These materials are absorbed topically relatively easily, and, by a variety of mechanisms, achieve permeation enhancement for some drugs. Ethanol (Gale et. al., U.S. Pat. No. 4,615,699 and Campbell et. al., U.S. Pat. Nos. 4,460,372 and 4,379,454), dimethyl sulfoxide (US 3,740,420 and 3,743,727, and US 4,575,515), and glycerine derivatives (US 4,322,433) are a few examples of compounds which have shown an ability to enhance the absorption of various compounds.

The pharmaceutical compositions of the invention can also be intended for administration with aerosolized formulation to target areas of a patient's respiratory tract.

Devices and methodologies for delivering aerosolized bursts of a formulation of a drug is disclosed in US 5,906,202. Formulations are preferably solutions, e.g. aqueous solutions, ethanoic solutions, aqueous/ethanoic solutions, saline solutions, colloidal suspensions and microcrystalline suspensions. For example aerosolized particles comprise the active ingredient mentioned above and a carrier, (e.g., a pharmaceutically active respiratory drug and carrier) which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a flexible porous membrane. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs.

The invention encompasses the systems described in US 5,556,611:

- liquid gas systems (a liquefied gas is used as propellent gas (e.g. low-boiling FCHC or propane, butane) in a pressure container,
- suspension aerosol (the active substance particles are suspended in solid form in the liquid propellent phase),
- pressurized gas system (a compressed gas such as nitrogen, carbon dioxide, dinitrogen monoxide, air is used.

Thus, according to the invention the pharmaceutical preparation is made in that the active substance is dissolved or dispersed in a suitable nontoxic medium and said solution or dispersion atomized to an aerosol, i.e. distributed extremely finely in a carrier gas. This is technically possible for example in the form of aerosol propellent gas packs, pump aerosols or other devices known per se for liquid misting and solid atomizing which in particular permit an exact individual dosage.

Therefore, the invention is also directed to aerosol devices comprising the compound as defined above and such a formulation, preferably with metered dose valves.

The pharmaceutical compositions of the invention can also be intended for intranasal administration.

In this regard, pharmaceutically acceptable carriers for administering the compound to the nasal mucosal surfaces will be readily appreciated by the ordinary artisan. These carriers are described in the Remington's Pharmaceutical Sciences" 16th edition, 1980, Ed. By Arthur Osol, the disclosure of which is incorporated herein by reference.

The selection of appropriate carriers depends upon the particular type of administration that is contemplated. For administration via the upper respiratory tract, the composition can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension, for intranasal administration as drops or as a spray. Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from pH 6.0 to pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's, Id. at page 1445). Of course, the ordinary artisan can readily determine a suitable saline content and pH for an innocuous aqueous carrier for nasal and/or upper respiratory administration.

Common intranasal carriers include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 3000 cps, or from about 2500 to 6500 cps, or greater, may also be used to provide a more sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington's, cited supra. A preferred alkylcellulose is, e.g., methylcellulose in a concentration ranging from about 5 to about 1000 or more mg per

100 ml of carrier. A more preferred concentration of methyl cellulose is, simply by way of example, from about 25 to about mg per 100 ml of carrier.

Other ingredients, such as art known prescrvatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. For nasal administration of solutions or suspensions according to the invention, various devices are available in the art for the generation of drops, droplets and sprays.

A premeasured unit dosage dispenser including a dropper or spray device containing a solution or suspension for delivery as drops or as a spray is prepared containing one or more doses of the drug to be administered and is another object of the invention. The invention also includes a kit containing one or more unit dehydrated doses of the compound, together with any required salts and/or buffer agents, preservatives, colorants and the like, ready for preparation of a solution or suspension by the addition of a suitable amount of water.

Another aspect of the invention is directed to the use of said compound to manufacture a medicament. In other words, the invention embraces a method for treating a disease related to unregulated c-kit transduction comprising administering an effective amount of a compound as defined above to a mammal in need of such treatment.

More particularly, the invention is aimed at a method for treating a disease selected from autoimmune diseases, allergic diseases, bone loss, cancer such as leukemia and GIST, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases (IBD), interstitial cystitis, mastocytosis, infections diseases, metabolic disorders, fibrosis,

diabetes and CNS disorders comprising administering an effective amount a compound depicted above to a mammal in need of such treatment.

The above described compounds are useful for manufacturing a medicament for the treatment of diseases related to unregulated c-kit transduction, including, but not limited to:

- neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas.
- tumor angiogenesis.
- metabolic diseases such as diabetes mellitus and its chronic complications; obesity; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.
- allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and blood sucking parasitic infestation.
- interstitial cystitis.
- bone loss (osteoporosis).
- inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.
- autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's

syndrome, nodular panarteritis, autoimmune enteropathy, as well as proliferative glomerulonephritis.

- graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.
- Other autoimmune diseases embraced by the invention active chronic hepatitis and chronic fatigue syndrome.
- subepidermal blistering disorders such as pemphigus.
- Vasculitis.
- melanocyte dysfunction associated diseases such as hypermelanosis resulting from melanocyte dysfunction and including lentigines, solar and senile lentigo, Dubreuilh melanosis, moles as well as malignant melanomas. In this regard, the invention embraces the use of the compounds defined above to manufacture a medicament or a cosmetic composition for whitening human skin.
- CNS disorders such as psychiatric disorders, migraine, pain, memory loss and nerve cells degeneracy. More particularly, the method according to the invention is useful for the treatment of the following disorders: Depression including dysthymic disorder, cyclothymic disorder, bipolar depression, severe or "melancholic" depression, atypical depression, refractory depression, seasonal depression, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, other syndromes such as mental slowing and loss of concentration, pessimistic worry, agitation, self-deprecation, decreased libido, pain including, acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain, psychogenic pain syndromes, anxiety disorders including anxiety associated with hyperventilation and cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, psychiatric emergencies such as panic attacks, including psychosis, delusional disorders, conversion disorders, phobias, mania, delirium, dissociative episodes including dissociative amnesia,

dissociative fugue and dissociative identity disorder, depersonalization, catatonia, seizures, severe psychiatric emergencies including suicidal behaviour, self-neglect, violent or aggressive behaviour, trauma, borderline personality, and acute psychosis, schizophrenia including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia,

- neurodegenerative diseases including Alzheimer's disease , Parkinson's disease, Huntington's disease, the prion diseases, Motor Neurone Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).
- substance use disorders as referred herein include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.

Regarding mastocytosis, the invention contemplates the use of the compounds as defined above for treating the different categories which can be classified as follows:

The category I is composed by two sub-categories (IA and IB). Category IA is made by diseases in which mast cell infiltration is strictly localized to the skin. This category represents the most frequent form of the disease and includes : i) urticaria pigmentosa, the most common form of cutaneous mastocytosis, particularly encountered in children, ii) diffuse cutaneous mastocytosis, iii) solitary mastocytoma and iv) some rare subtypes like bullous, erythrodermic and teleangiectatic mastocytosis. These forms are characterized by their excellent prognosis with spontaneous remissions in children and a very indolent course in adults. Long term survival of this form of disease is generally comparable to that of the normal population and the translation into another form of mastocytosis is rare. Category IB is represented by indolent systemic disease (SM) with or without cutaneous involvement. These forms are much more usual in adults than in children. The course of the disease is often indolent, but sometimes signs of aggressive or malignant mastocytosis can occur, leading to progressive impaired organ function.

The category II includes mastocytosis with an associated hematological disorder, such as a myeloproliferative or myelodysplastic syndrome, or acute leukemia. These malignant mastocytosis does not usually involve the skin. The progression of the disease depends generally on the type of associated hematological disorder that conditiones the prognosis.

The category III is represented by aggressive systemic mastocytosis in which massive infiltration of multiple organs by abnormal mast cells is common. In patients who pursue this kind of aggressive clinical course, peripheral blood features suggestive of a myeloproliferative disorder are more prominent. The progression of the disease can be very rapid, similar to acute leukemia, or some patients can show a longer survival time.

Finally, the category IV of mastocytosis includes the mast cell leukemia, characterized by the presence of circulating mast cells and mast cell progenitors representing more than 10% of the white blood cells. This entity represents probably the rarest type of leukemia in humans, and has a very poor prognosis, similar to the rapidly progressing variant of malignant mastocytosis. Mast cell leukemia can occur either *de novo* or as the terminal phase of urticaria pigmentosa or systemic mastocytosis.

The invention also contemplates the method as depicted for the treatment of recurrent bacterial infections, resurging infections after asymptomatic periods such as bacterial cystitis. More particularly, the invention can be practiced for treating FimH expressing bacteria infections such as Gram-negative enterobacteria including *E. coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobactor freudii* and *Salmonella typhimurium*.

In this method for treating bacterial infection, separate, sequential or concomitant administration of at least one antibiotic selected bacitracin, the cephalosporins, the penicillins, the aminoglycosides, the tetracyclines, the streptomycins and the macrolide

antibiotics such as erythromycin; the fluoroquinolones, actinomycin, the sulfonamides and trimethoprim, is of interest.

FIGURE LEGENDS

Figures 1A and 1B: Inhibition of c-kit

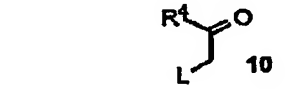
A- Inhibition of the Ba/F3 cell line proliferation. This cell line is expressing the juxtamembrane mutation KitΔ27. Comparison with lines expressing Kit wild (Ba/F3 Kit) cultured with the Kit ligand (KL) or with IL3 and comparison with lines expressing an activating mutation in the distal domain of Kit (Ba/F3 Kit814) or the Bcr-Abl oncogene (Ba/F3 Bcr-Abl). The proliferation rate is determined with the incorporation of tritiated thymidine of 10^4 cells/wells in a microplaque 96 after two days of culture in presence of different concentrations of the AB-1010 compound.

B- **Activity of AB 1010 versus other tyrosine kinase inhibitors on Bcr-Abl.** This figure shows that AB-1010 is not active on Bcr-Abl whereas STI 571 display an activity. AB-1010 has therefore a better specificity on c-kit.

Figure 2: Inhibition of the phosphorylation of KIT wild or KIT mutated in juxtamembrane domain (KITΔ27) by AB 1010 compared to STI 571.
The Ct line is used as a negative control (Ba/F3 line that does not express Kit). Molecular Weights are indicated on the left in Kda. We used antibodies from rabbit immuno-serum of anti mc-Kit and the monoclonal antibody 4G10 anti Phospho-Tyrosine (PY). Stimulation time with the Kit ligand is 5 minutes at 37°C at a concentration of 250ng/ml.

Example 1: Compound synthesis

The compounds described in the present invention may be synthesized according to standard techniques. The general approach to the synthesis of compounds of formula I involves the condensation of a derivative 10 of a methyl ketone with a thiourea of the type 11 or 12.



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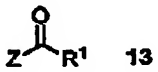

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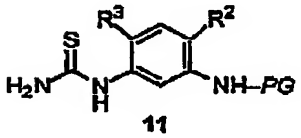

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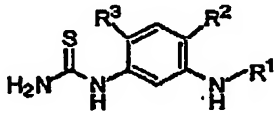

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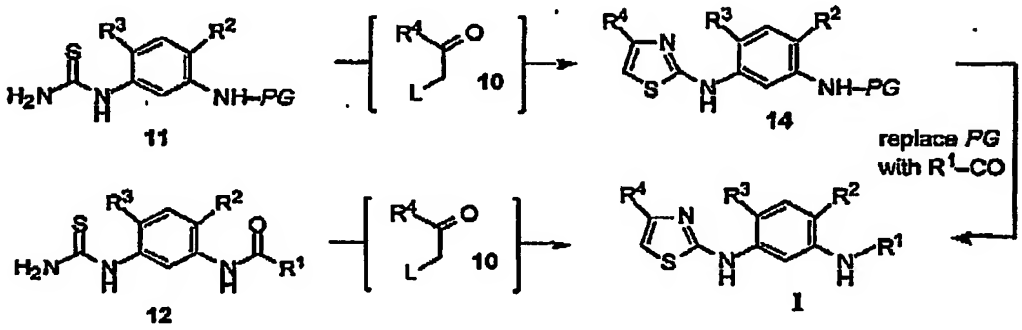
Substituent L in formula 10 represents a nucleofugal leaving group active in nucleophilic substitution reactions. Examples of L are chloro, bromo, iodo, toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, etc., with L being preferentially a bromo group.

Thioureas 11 and 12 differ in that one of the nitrogen atoms connected to the central ring in 11 is blocked with an appropriate protecting group, *PG*, of a type commonly utilized by the person skilled in the art, whereas the corresponding nitrogen atom of 12 already bears the unit R^1–CO required in the final product.

Syntheses employing thioureas such as 11 proceed in such a manner that the protecting group *PG* will be replaced with the segment represented by the unit R^1–CO at an appropriate operational stage, according to the synthesis flowchart shown below. The introduction of the R^1–CO unit requires the use of a reactant derived from a carboxylic acid and generally described by chemical formula 13, wherein Z may be OH, O-Alkyl,

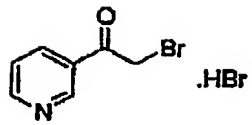
O-Aryl, S-Alkyl, S-Aryl, or Halogen. Alternatively, syntheses employing thioureas of the type 12 directly furnish the final compounds.



The following experimental procedure represents a typical preferred method for the synthesis of compounds of formula I.

General: All chemicals used were commercial reagent grade products. Dimethylformamide (DMF), methanol (MeOH) were of anhydrous commercial grade and were used without further purification. Dichloromethane and tetrahydrofuran (THF) were freshly distilled under a stream of argon before use. The progress of the reactions was monitored by thin layer chromatography using precoated silica gel 60F 254, Fluka TLC plates, which were visualized under UV light. Multiplicities in ^{1}H NMR spectra are indicated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quadruplet (q), and multiplet (m) and the NMR spectrum were realized on a 300MHz Bruker spectrometer.

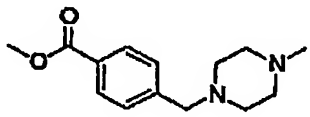
3-Bromoacetyl-pyridine, HBr salt



Dibromine (17.2g, 108 mmol) was added dropwise to a cold (0°C) solution of 3-acetyl-pyridine (12 g, 99 mmol) in acetic acid containing 33% of HBr (165 mL) under vigourous stirring. The vigorously stirred mixture was warmed to 40°C for 2h and then to 75°C. After 2h at 75°C, the mixture was cooled and diluted with ether (400 mL) to precipitate the product. which was recovered by filtration and washed with ether and acetone to give white crystals (100%). This material may be recrystallised from methanol and ether.

IR (neat) : 3108, 2047,2982, 2559, 1709, 1603, 1221, 1035, 798 cm^{-1} - ^1H NMR (DMSO-d^6) δ = 5.09 (s, 2H, CH_2Br) ; 7.88 (m, 1H, pyridyl-H) ; 8.63 (m, 1H, pyridyl-H) ; 8.96 (m, 1H, pyridyl-H) ; 9.29 (m, 1H, pyridyl-H).

Methyl -[4-(1-N-methyl-piperazino)-methyl]-benzoate

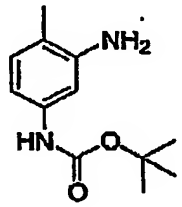


To methyl-4-formyl benzoate (4.92 g, 30 mmol) and N-methyl-piperazine (3.6 mL, 32 mmol) in acetonitrile (100 mL) was added dropwise 2.5 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1h. After slow addition of sodium cyanoborohydride (2 g, 32 mmol), the solution was left stirring overnight at room temperature. Water (10 mL) was then added to the mixture, which was further acidified with 1N HCl to pH=6-7. The acetonitrile was removed under reduced pressure and the residual aqueous solution was extracted with diethyl ether (4x30 mL). These extracts

were discarded. The aqueous phase was then basified (pH>12) by addition of 2.5N aqueous sodium hydroxyde solution. The crude product was extracted with ethyl acetate (4×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a slightly yellow oil which became colorless after purification by Kugelrohr distillation (190°C) in 68% yield.

IR(neat) : 3322, 2944, 2802, 1721, 1612, 1457, 1281, 1122, 1012 - ^1H NMR ($CDCl_3$) δ = 2.27 (s, 3H, NCH_3); 2.44 (m, 8H, 2×NCH_2CH_2N); 3.53 (s, 2H, $ArCH_2N$); 3.88 (s, 3H, OCH_3); 7.40 (d, 2H, *J*= 8.3 Hz,2×ArH); 7.91 (d, 2H, *J*= 8.3 Hz, 2×ArH) - ^{13}C NMR ($CDCl_3$) δ = 45.8 (NCH_3); 51.8 (OCH_3); 52.9 (2×CH_2N); 54.9 (2×CH_2N); 62.4 ($ArCH_2N$); 128.7 (2×ArC); 129.3 (2×ArC); 143.7(ArC); 166.7 ($ArCO_2CH_3$) - MS CI (m/z) (%) : 249 (M+1, 100%).

2-Methyl-5-tert-butoxycarbonylamino-aniline



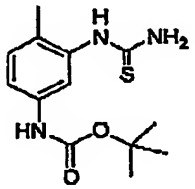
A solution of di-tert-butyldicarbonate (70 g, 320 mmol) in methanol (200 mL) was added over 2 h to a cold (–10°C) solution of 2,4-diaminotoluene (30 g, 245 mmol) and triethylamine (30 mL) in methanol (15 mL). The reaction was followed by thin layer chromatography (hexane/ethyl acetate, 3 :1) and stopped after 4h by adding 50 mL of water. The mixture was concentrated in vacuo and the residue was dissolved in 500 mL of ethyl acetate. This organic phase was washed with water (1×150 mL) and brine (2×150 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting

light brown solid was washed with small amounts of diethyl ether to give off-white crystals of 2-methyl-5-tert-butoxycarbonylamino-aniline in 67% yield.

IR (neat) : 3359 ; 3246 ; 2970 ; 1719 ; 1609 ; 1557 ; 1173 ; 1050 cm^{-1}- ^1H NMR ($CDCl_3$): δ = 1.50 (s, 9H, tBu); 2.10 (s, 3H, $ArCH_3$); 3.61 (br s, 2H, NH_2); 6.36 (br s, 1H, NH); 6.51 (dd, 1H, *J* = 7.9 Hz, 2.3 Hz, ArH); 6.92 (d, 1H, J= 7.9 Hz, ArH); 6.95 (s, 1H, ArH) - ^{13}C NMR ($CDCl_3$) δ = 16.6 ($ArCH_3$); 28.3 ($C(CH_3)_3$); 80.0 ($C(CH_3)_3$); 105.2 (ArC); 108.6 (ArC); 116.9 (ArC); 130.4 (ArC-CH_3); 137.2 (ArC-NH); 145.0 (ArC-NH_2); 152.8 (COOtBu)

MS ESI (m/z) (%) : 223 (M+1), 167 (55, 100%).

N-(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea

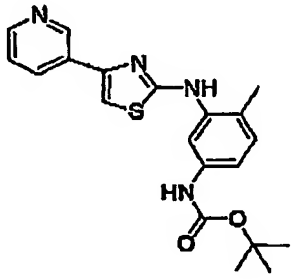


Benzoyl chloride (5.64 g, 80 mmol) was added dropwise to a well-stirred solution of ammonium thiocyanate (3.54 g, 88 mmol) in acetone (50 mL). The mixture was refluxed for 15 min, then, the hydrobromide salt of 2-methyl-5-tert-butoxycarbonylamino-aniline (8.4g, 80 mmol) was added slowly portionswise. After 1h, the reaction mixture was poured into ice-water (350 mL) and the bright yellow precipitate was isolated by filtration. This crude solid was then refluxed for 45 min in 70 mL of 2.5 N sodium hydroxide solution. The mixture was cooled down and basified with ammonium hydroxide. The precipitate of crude thiourea was recovered by filtration and dissolved in 150 mL of ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4,

and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate, 1 :1) to afford 63 % of *N* -(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea as a white solid.

IR (ncat) : 3437, 3292, 3175, 2983, 1724, 1616, 1522, 1161, 1053 cm^{-1}- ^1H NMR (DMSO-d^6) δ = 1.46 (s, 9H, tBu) ; 2.10 (s, 3H, $ArCH_3$) ; 3.60 (br s, 2H, NH_2) ; 7.10 (d, 1H, J = 8.29 Hz, ArH) ; 7.25 (d, 1H, J = 2.23 Hz, ArH) ; 7.28 (d, 1H, J = 2.63 Hz, ArH) ; 9.20 (s, 1H, ArNH) ; 9.31 (s, 1H, ArNH) - ^{13}C NMR (DMSO-d^6) δ = 25.1 ($ArCH_3$); 28.1 ($C(CH_3)_3$); 78.9 ($C(CH_3)_3$); 116.6 (ArC); 117.5 (ArC); 128.0 (ArC); 130.4 (ArC-CH_3); 136.5 (ArC-NH); 137.9 (ArC-NH); 152.7 (COOtBu); 181.4 (C=S) - MS CI(m/z) : 282 (M+1, 100%) ; 248 (33) ; 226 (55) ; 182 (99) ; 148 (133) ; 93 (188).

2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole

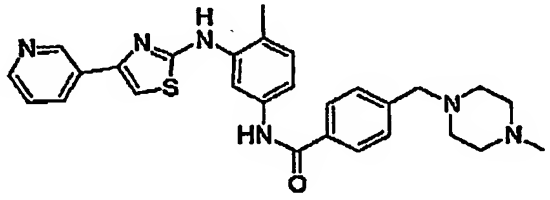


A mixture of 3-bromoacetyl-pyridine, HBr salt (0.81g, 2.85 mmol), *N* -(2-methyl-5-tert-butoxycarbonylamino)phenyl-thiourea (0.8g, 2.85 mmol) and $KHCO_3$ (~0.4g) in ethanol (40 mL) was heated at 75°C for 20h. The mixture was cooled, filtered (removal of $KHCO_3$) and evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (40 mL) and washed with saturated aqueous sodium hydrogen carbonate solution and with water. The organic layer was dried over Na_2SO_4 and concentrated. Colum

chromatographic purification of the residue (hexane/ethyl acetate, 1 :1) gave the desired thiazole in 70% yield as an orange solid

IR(neat) : 3380, 2985, 2942, 1748, 1447, 1374, 1239, 1047, 938 - ^{1}H NMR ($CDCl_3$) δ = 1.53 (s, 9H, tBu) ; 2.28 (s, 3H, $ArCH_3$) ; 6.65 (s, 1H, thiazole-H) ; 6.89 (s, 1H) ; 6.99 (dd, 1H, J= 8.3 Hz, 2.3 Hz) ; 7.12 (d, 2H, J=8.3 Hz) ; 7.35 (dd, 1H, J = 2.6 Hz, 4.9 Hz) ; 8.03 (s, 1H) ; 8.19 (dt, 1H, J= 1.9 Hz, 7.9 Hz) ; 8.54 (br s, 1H, NH) ; 9.09 (s, 1H, NH) - ^{13}C NMR ($CDCl_3$) δ = 18.02 ($ArCH_3$) ; 29.2 ($C(CH_3)_3$) ; 81.3 ($C(CH_3)_3$) ; 104.2 (thiazole-C) ; 111.6 ; 115.2 ; 123.9 ; 124.3 ; 131.4 ; 132.1 ; 134.4 ; 139.5 ; 148.2 ; 149.1 ; 149.3 ; 153.6 ; 167.3 (C=O) - MS CI (m/z) (%) : 383 (M+1, 100%) ; 339 (43) ; 327 (55) ; 309 (73) ; 283 (99) ; 71 (311).

AB-1010



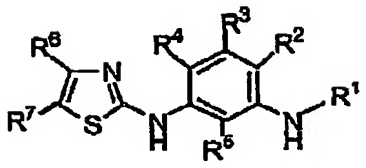
2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole (0.40g, 1.2 mmol) was dissolved in 10 mL of 20% TFA/CH_2Cl_2. The solution was stirred at rool temperature for 2h, then it was evaporated under reduced pressure. The residue was dissolved in ethyl acetate. The organic layer was washed with aqueous 1N sodium hydroxide solution, dried over $MgSO_4$, and concentrated to afford 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole as a yellow-orange solid in 95% yield. This crude product was used directly in the next step.

A 2M solution of trimethyl aluminium in toluene (2.75 mL) was added dropwise to a cold (0° C) solution of 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole (0.42 g, 1.5 mmol) in anhydrous dichloromethane (10 mL) under argon atmosphere. The mixture was warmed to romm temperature and stirred at room temperature for 30 min. A solution of methyl-4-(1-N-methyl-piperazino)-methyl benzoate (0.45 g, 1.8 mmol) in anhydrous dichloromethane (1 mL) and added slowly, and the resulting mixture was heated at reflux for 5h. The mixture was cooled to 0°C and quenched by dropwise addition of a 4N aqueous sodium hydroxide solution (3 mL). The mixture is extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (3×20 mL) and dried over anhydrous $MgSO_4$. AB1010 is obtained in 72% after purification by column chromatography (dichloromethane/ methanol, 3 :1)

IR (neat) : 3318, 2926, 1647, 1610, 1535, 1492, 1282, 1207, 1160, 1011, 843 - ^{1}H NMR ($CDCl_3$) δ = 2.31 (br s, 6H, $ArCH_3$+NCH_3) ; 2.50 (br s, 8H, 2×NCH_2CH_2N) ; 3.56 (s, 2H, $ArCH_2N$) ; 6.89 (s, 1H, thiazoleH) ; 7.21-7.38 (m, 4H); 7.45 (m, 2H) ; 7.85 (d, 2H, J = 8.3Hz) ; 8.03 (s, 1H) ; 8.13 (s, 1H) ; 8.27 (s, 1H) ; 8.52 (br s, 1H) ; 9.09 (s, 1H, NH) - ^{13}C NMR ($CDCl_3$) δ = 17.8 ($ArCH_3$) ; 46.2 (NCH_3) ; 53.3 (NCH_2) ; 55.3 (NCH_2) ; 62.8 ($ArCH_2N$) ; 99.9 (thiazole-C) ; 112.5 ; 123.9 ; 125.2 ; 127.5 ; 129.6 ; 131.6 ; 133.7 ; 134.0 ; 137.6 ; 139.3 ; 142.9 ; 148.8 ; 149.1 ; 166.2 (C=O) ; 166.7 (thiazoleC-NH) - MS CI (m/z) (%) : 499 (M+H, 100%) ; 455 (43) ; 430 (68) ; 401 (97) ; 374 (124) ; 309 (189) ; 283 (215) ; 235 (263) ; 121 (377) ; 99 (399).

CLAIMS

1. A compound of formula I:



FORMULA I

wherein R^1 is:

a) a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality;

b) an aryl or heteroaryl group optionally substituted by an alkyl or aryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

c) a sulfonyl or a -SO2-R group wherein R is an alkyl, aryl or heteroaryl substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

d) a -CO-NH-R, -CO-R, -CO-OR or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl, heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality;

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy,

iv) H, an halogen selected from I, F, Cl or Br; NH2, NO2 or SO2;

and R^7 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

iv) H, an halogen selected from I, F, Cl or Br; NH2, NO2 or SO2.

2. A compound according to claim 1 selected from:

4-Diethylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-morpholin-4-ylmethyl-benzamide,

4-Dipropylaminomethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-piperidin-1-ylmethyl-benzamide,

3-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

4-Hydroxymethyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

4-{[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylamino]-methyl}-benzoic acid methyl ester,

3-Phenyl-propynoic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide,

4-Amino-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

2-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

4-(3-{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl}-ureido)-benzoic acid ethyl ester,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureido]-benzamide,

4-[3-(4-Bromo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

{4-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-benzyl}-carbamic acid tert-butyl ester,

4-Hydroxy-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide

4-[(Diisopropylamino)-methyl]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-(3-thiophen-2-yl-ureido)-benzamide,

4-[3-(3,5-Dimethyl-isoxazol-4-yl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

4-[3-(4-Methoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

4-[3-(4-Difluoromethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

Thiophene-2-sulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester,

4-Iodo-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-pyrrolidin-1-ylmethyl-benzamide,

3-Methyl-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-trifluoromethyl-benzamide,

4-[3-(2,4-Dimethoxy-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(4-trifluoromethyl-phenyl)-ureidomethyl]-benzamide,

N-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-4-[3-(3,4,5-trimethoxy-phenyl)-ureido]-benzamide,

4-[3-(2-Iodo-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

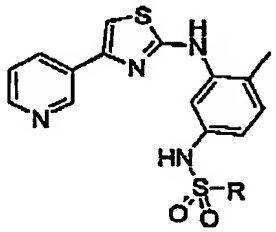
4-[3-(4-Fluoro-phenyl)-ureido]-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide,

2-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester,

3-Fluoro-benzenesulfonic acid 4-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenylcarbamoyl]-phenyl ester,

and 2-(2-methyl-5-tert-butoxycarbonylamino)phenyl-4-(3-pyridyl)-thiazole.

3. A compound according to claim 1 of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality, or an aryl or heteroaryl group optionally substituted by an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

4. A compound according to claim 3 selected from :

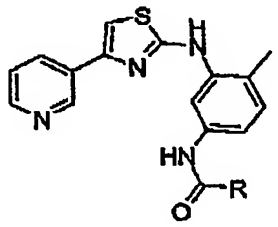
3-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzenesulfonamide,

2-Fluoro-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzenesulfonamide,

Thiophene-2-sulfonic acid [4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-amide,

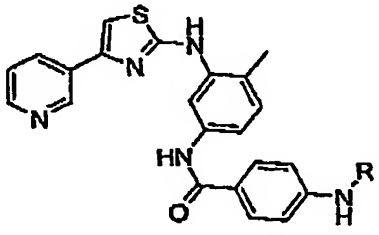
and 4-Iodo-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzenesulfonamide.

5. A compound according to claim 1 of the following formula:



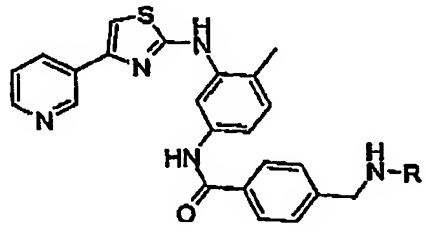
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

6. A compound according to claim 1 of the following formula:



wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a a cycloalkyl, an aryl or heteroaryl group optionally substituted with a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;
a sulfonyl or a -SO2-R group wherein R is H, an alkyl, cycloalkyl, aryl or heteroaryl optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H, an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality.

7. A compound according to claim 1 of the following formula:



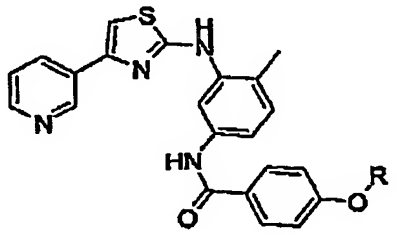
wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality; a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or

bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a sulfonyl or a -SO2-R group wherein R is H or an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality.

8. A compound according to claim 1 of the following formula:

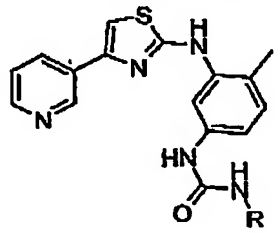


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F, or bearing a pendant basic nitrogen functionality;

a cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or an alkyl, cycloalkyl, aryl or heteroaryl group substituted by a alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality;

a sulfonyl or a -SO2-R group wherein R is H or an alkyl, cycloalkyl, aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a –CO-R or a -CO-NRR' group, wherein R and R' are independently chosen from H or an aryl heteroaryl, alkyl and cycloalkyl group optionally substituted with at least one heteroatom or bearing a pendant basic nitrogen functionality.

9. A compound according to claim 1 of the following formula:

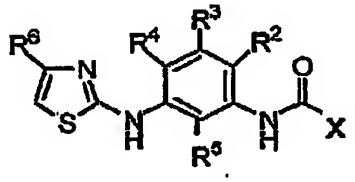


wherein R is H or an organic group that can be selected for example from a linear or branched alkyl group containing from 1 to 10 carbon atoms optionally substituted with at least one heteroatom (for example an halogen) or bearing a pendant basic nitrogen functionality; a cycloalkyl, an aryl or heteroaryl group optionally substituted with at least one heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality; or a cycloalkyl, an aryl or heteroaryl group substituted by an alkyl, a cycloalkyl, an aryl or heteroaryl group optionally substituted with an heteroatom, notably a halogen selected from I, Cl, Br and F or bearing a pendant basic nitrogen functionality.

10. A compound according to claim 9 selected from:
1-(4-Methoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-(4-Bromo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,

1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(4-trifluoromethyl-phenyl)-urea,
1-(4-Fluoro-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-urea,
4-{3-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-ureido}-benzoic acid ethyl ester,
1-[4-Methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-3-thiophen-2-yl-urea,
1-Cyclohexyl-1-(N-Cyclohexyl-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-(2,4-Dimethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-(2-Iodo-phenyl)-1-(N-(2-Iodo-phenyl)-formamide)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-(3,5-Dimethyl-isoxazol-4-yl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-(2-Iodo-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
1-(4-Difluoromethoxy-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea,
and 1-(4-Dimethylamino-phenyl)-3-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-urea.

11. A compound according to claim 1 of formula II:



FORMULA II

wherein X is R or NRR' and wherein R and R' are independently chosen from H, an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality; or an aryl, an heteroaryl, an alkyl and a cycloalkyl group substituted with an aryl, an heteroaryl, an alkyl and a cycloalkyl group optionally substituted with at least one heteroatom, such as for example a halogen chosen from F, I, Cl and Br and optionally bearing a pendant basic nitrogen functionality,

R^2 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^3 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^4 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

R^5 is hydrogen, halogen or a linear or branched alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl or alkoxy;

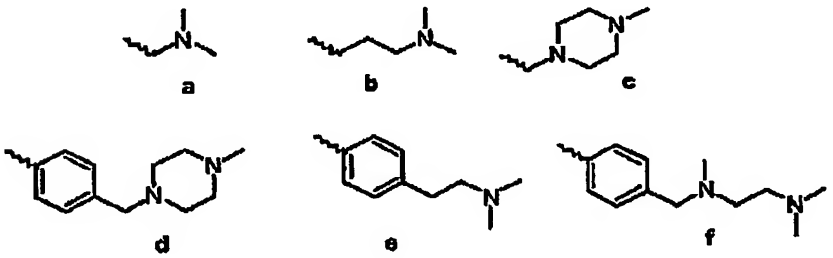
R^6 is one of the following:

(i) an aryl group such as phenyl or a substituted variant thereof bearing any combination, at any one ring position, of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy;

(ii) a heteroaryl group such as a 2, 3, or 4-pyridyl group, which may additionally bear any combination of one or more substituents such as halogen, alkyl groups containing from 1 to 10 carbon atoms, trifluoromethyl and alkoxy;

(iii) a five-membered ring aromatic heterocyclic group such as for example 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, which may additionally bear any combination of one or more substituents such as halogen, an alkyl group containing from 1 to 10 carbon atoms, trifluoromethyl, and alkoxy.

12. A compound according to claim 11, wherein X is a substituted alkyl, aryl or heteroaryl group bearing a pendant basic nitrogen functionality represented for example by the structures a to f shown below, wherein the wavy line corresponds to the point of attachment to core structure of formula II :



13. A compound according to claim 11, wherein X is group d and R^6 is a 3-pyridyl group.

14. A compound according to claim 11, wherein X is group d and R^4 is a methyl group.

15. A compound according to claim 11, wherein X is group d and R^2 and/or R^3 and/or R^5 is H.

16. A compound according to claim 1 or 11, wherein R^6 is a 3-pyridyl group and R^4 is a methyl group.

17. A compound according to claim 1 or 11, wherein R^6 is a 3-pyridyl group and R^2 and/or R^3 and/or R^5 is H.

18. A compound according to claim 1 or 11, wherein R^2 and/or R^3 and/or R^5 is H and R^4 is a methyl group.

19. A compound according to claim 1 or 11, wherein R^2 and/or R^3 and/or R^5 is H, R^4 is a methyl group and R^6 is a 3-pyridyl group.

20. A compound according to claim 11, which is the 2-(2-methyl-5-amino)phenyl-4-(3-pyridyl)-thiazole.

21. A pharmaceutical composition comprising a compound according to one of claims 1 to 20.

22. A pharmaceutical composition according to claim 21 further comprising a pharmaceutically acceptable carrier.

23. A pharmaceutical composition according to claim 21 formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, and suspensions.

24. A cosmetic composition for topical administration comprising a compound according to one of claims 1 to 20.

25. Use of a compound according to one of claims 1 to 20 to manufacture a medicament.

26. Use of a compound according to one of claims 1 to 20 to manufacture a medicament for treating a disease selected from:

- neoplastic diseases such as mastocytosis, canine mastocytoma, human gastrointestinal stromal tumor ("GIST"), small cell lung cancer, non-small cell lung cancer, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, colorectal carcinomas, gastric carcinomas, gastrointestinal stromal tumors, testicular cancers, glioblastomas, and astrocytomas.
- tumor angiogenesis.
- metabolic diseases such as diabetes mellitus and its chronic complications; obesity; hyperlipidemias and dyslipidemias; atherosclerosis; hypertension; and cardiovascular disease.
- allergic diseases such as asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and blood sucking parasitic infestation.
- interstitial cystitis.
- bone loss (osteoporosis).
- inflammatory diseases such as rheumatoid arthritis, conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.
- autoimmune diseases such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis and polyarthritis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus

erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune-enteropathy, as well as proliferative glomerulonephritis.

- graft-versus-host disease or graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung, and bone marrow.
- Other autoimmune diseases embraced by the invention active chronic hepatitis and chronic fatigue syndrome.
- subepidermal blistering disorders such as pemphigus.
- Vasculitis.
- melanocyte dysfunction associated diseases such as hypermelanosis resulting from melanocyte dysfunction and including lentigines, solar and senile lentigo, Dubreuilh melanosis, moles as well as malignant melanomas. In this regard, the invention embraces the use of the compounds defined above to manufacture a medicament or a cosmetic composition for whitening human skin.
- CNS disorders such as psychiatric disorders, migraine, pain, memory loss and nerve cells degeneracy. More particularly, the method according to the invention is useful for the treatment of the following disorders: Depression including dysthymic disorder, cyclothymic disorder, bipolar depression, severe or "melancholic" depression, atypical depression, refractory depression, seasonal depression, anorexia, bulimia, premenstrual syndrome, post-menopause syndrome, other syndromes such as mental slowing and loss of concentration, pessimistic worry, agitation, self-deprecation, decreased libido, pain including, acute pain, postoperative pain, chronic pain, nociceptive pain, cancer pain, neuropathic pain, psychogenic pain syndromes, anxiety disorders including anxiety associated with hyperventilation and cardiac arrhythmias, phobic disorders, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, psychiatric emergencies such as panic attacks, including psychosis, delusional disorders, conversion disorders,

phobias, mania, delirium, dissociative episodes including dissociative amnesia, dissociative fugue and dissociative identity disorder, depersonalization, catatonia, seizures, severe psychiatric emergencies including suicidal behaviour, self-neglect, violent or aggressive behaviour, trauma, borderline personality, and acute psychosis, schizophrenia including paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, and undifferentiated schizophrenia,

- neurodegenerative diseases including Alzheimer's disease , Parkinson's disease, Huntington's disease, the prion diseases, Motor Neurone Disease (MND), and Amyotrophic Lateral Sclerosis (ALS).
- substance use disorders as referred herein include but are not limited to drug addiction, drug abuse, drug habituation, drug dependence, withdrawal syndrome and overdose.

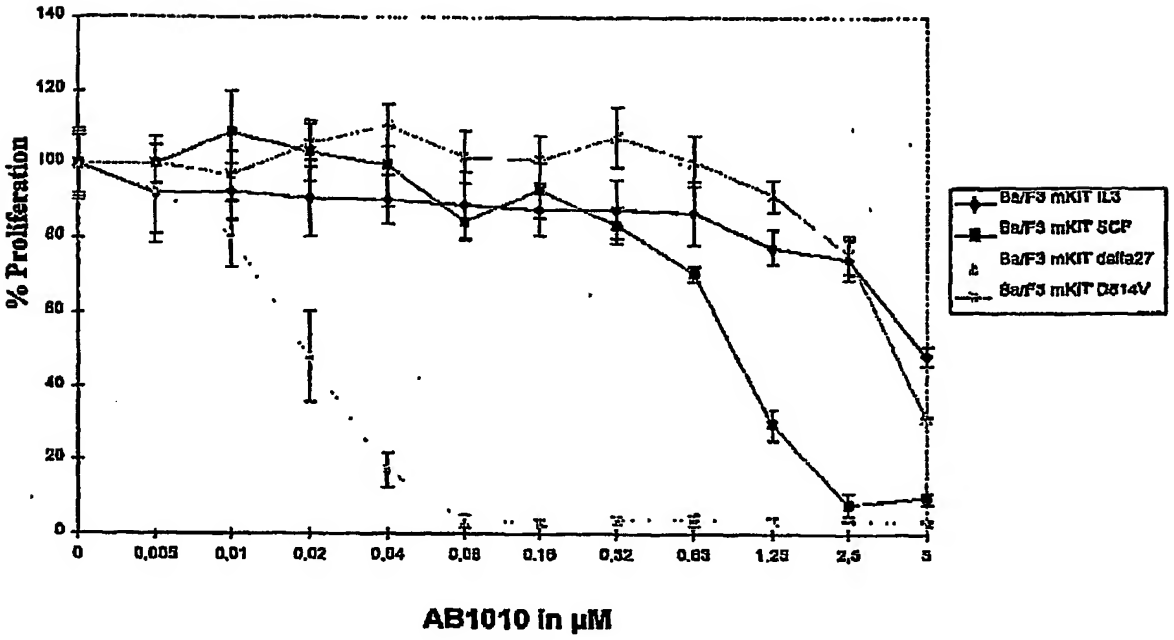


FIGURE 1A

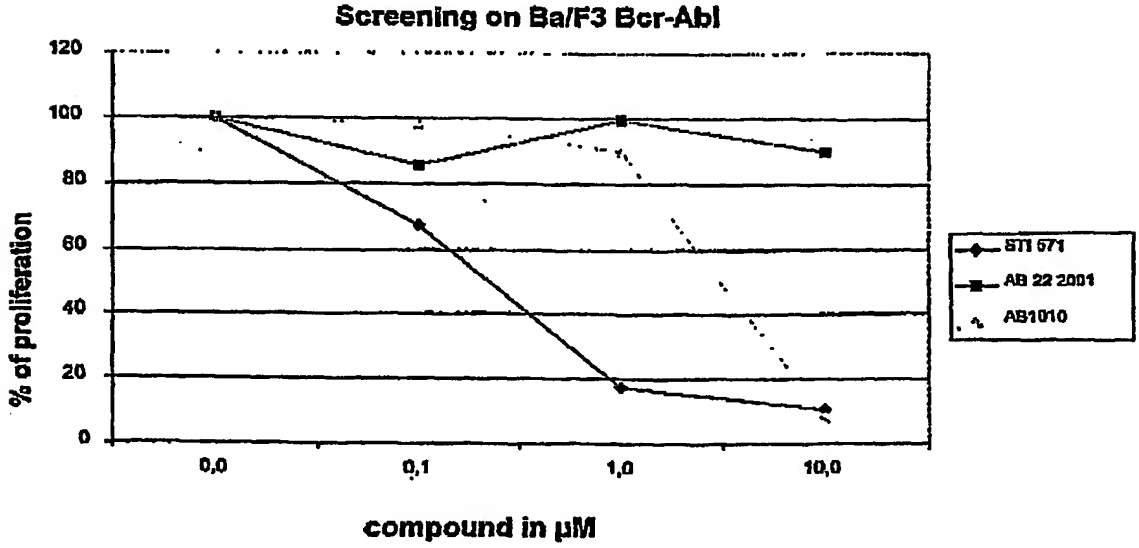


FIGURE 1B

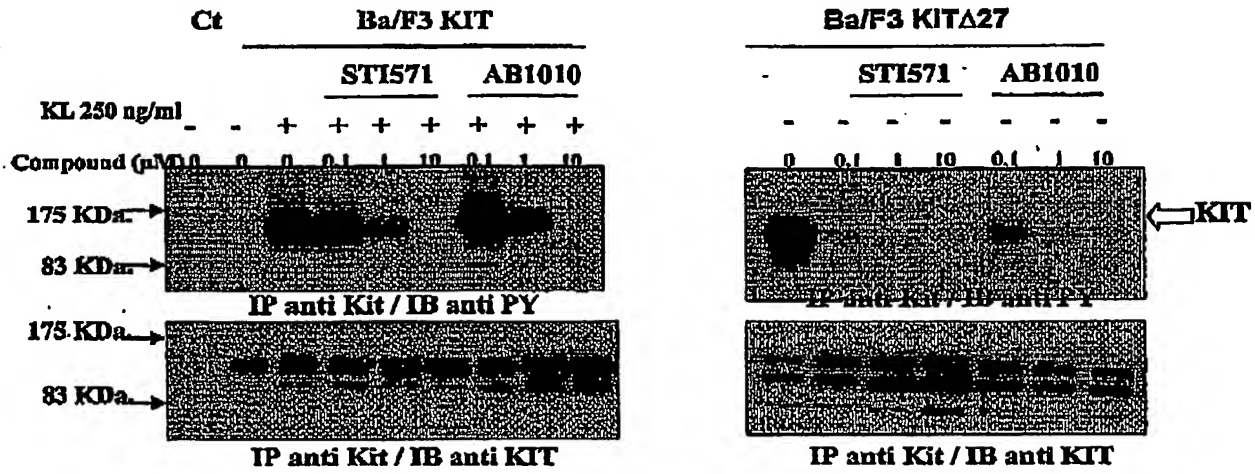

Ct
Ba/F3 KIT
Ba/F3 KITΔ27
STI571
AB1010
KL 250 ng/ml
Compound (μM)
175 KDa
83 KDa
IP anti Kit / IB anti PY
IP anti Kit / IB anti KIT
KIT

FIGURE 2